



DECLARATION  
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Vladimir Nikolaevich PAK, et al.

Serial No: 09/885,645

Group: 1642

Filed: June 20, 2001

Examiner: Susan Ungar

For: Method of treatment of malignant neoplasms and complex preparation having antineoplastic activity for use in such treatment

Attorney docket: U 014605-0

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

I, Vladimir Pak, a citizen of Russia, declare that:

I have PhD in Molecular Biology (1983, Institute of Bioorganic Chemistry of the Academy of Sciences, Moscow, Russia), MSc in Molecular Biology and Biochemistry (1979, Department of Natural Sciences, the Novosibirsk State University, Russia).

I have professional experience in Molecular Virology (Senior Researcher, Head of Laboratory in the United Scientific Research Institute of Molecular Biology), in Biotechnology (Head of Biotechnology Department at the Scientific-Industrial Company "Medical Technologies"), in Pharmacy (Head of Microbiology Department at Novosibirsk Pharmaceutical Plant).

I have been engaged in developing the present invention, I have directed and coordinated all the work in Novosibirsk. Thereafter I have consulted the licensee of the present invention, a firm Curonia (Estonia), and now I consult the instant licensee, a firm Celecure (Estonia).

I declare that during the treatment with the complex preparation Reducin no complications caused by the dextrans used have been observed. A rise in temperature and a shiver if observed during the treatment can be counteracted by standard medicines.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statement may jeopardize the validity of the application or any patent issued thereon.

Signed this 15<sup>th</sup> day of June, 2004

Signature:

Vladimir Pak



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The following experiments were conducted:

Example

Patient P., 62 years old, was hospitalized with the diagnosis: stomach cancer IV stage (T3N3M3) (adenocarcinoma, averagely differentiated), complicated with decompensation due to stenosis of the exit part of stomach.

The tumor was estimated as inoperable, but the patient was treated with palliative shunting: upper-median laparotomy. The inspection of the abdominal cavity organs showed metastases in the mesentery of colon, a lot of metastatic nodes of different sizes along the abdominal aorta, in the mesentery of small and large intestine, in the small epiploon, in the portal fissure, in the hepato-duodenal ligament. Subsequently metastases appeared in the front abdominal wall along the post-operational scar.

During the post-operational period chemotherapy was not used because of cachexy and intoxication.

Two months after the operation the patient was treated according to the present method. The complex preparation Reducin, comprising 0.075 mg of AFP, 6.0 mg of nystatin and 5.0 mg of glucose was injected by infusion in a course of 10 injections once in three days.

During the treatment with Reducin quality of life of the patient improved significantly: no fever, pains disappeared, appetite appeared, weight became stable, no syndrome of gastric dyspepsia, laboratory findings of blood were normal, skin metastases stopped to grow.

In order to stabilize the process and to retain satisfactory quality of life the treatment with Reducin was repeated after two months according to the same scheme (10 injections once in three days).

After the treatment with Reducin the patient lived for 1 year. The condition of the patient was stable without abrupt worsening. Satisfactory quality of life without using narcotic analgetics succeeded to retain for 10 months.

#### Example

Patient P., 59 years old, was hospitalized with the diagnosis: vulval cancer IV stage (highly differentiated, planocellular), metastases in the inguinal lymph nodes. Parallel diagnosis: chronic cholecystopancreatitis, chronic pyelonephritis, chronic bronchitis.

The patient had been operated on (expanded vulvectomy with two-sided inguinal-femoral lymphaden-ectomy) and treated with irradiation in the area of inguinal lymph nodes on the right side, in the area of vulva. This treatment was resultless. Intravenous polychemotherapy with adriamycin and cisplatin proved unsuccessful as well. After chemotherapy systemic inflammation and purulent intoxication appeared.

On receipt of the patient in hospital progression of the disease was observed. The patient was complaining pains in the lower extremities. The lymph nodes in groin area were enlarged, wherein fistulas with purulent exudate had been formed. Lymphatic stagnation in the right shank had led to the formation of lymphatic edema. The patient could not walk and was not able to serve herself. A rise in temperature up to 38°C was observed constantly.

After the course of preventive antibacterial and detoxifying therapy the patient was treated twice with Reducin at 1 month interval. The complex preparation Reducin, comprising 0.07 mg of AFP, 4.2 mg of amphotericin B and 5.0 mg of rheopolyglucin was injected by infusion in a course of 10 injections once in three days. During the treatment no side effects were registered.

The condition and feeling of the patient improved significantly, which became apparent from the disappearing of pains, from the stopping of secretion of purulent exudates from fistular paths in the inguinal area, from the decreasing of the sizes of tumorous nodes in the inguinal area, from the improving of appetite. The patient began to walk around indoors, she could serve herself and after the second course of the treatment with Reducin she began to walk outdoors.

One month after termination of the treatment with Reducin the condition of the patient worsened. Sepsis and polyorgan insufficiency became more acute again which led to the lethal end.

#### Example

Patient B., 43 years old, was hospitalized with the diagnosis: the right mammary gland cancer IV stage (T3N2M1).

The patient had previously been treated as follows: the right-hand mastectomy, six courses of polychemotherapy (CAMF), then tamoxifen, a course of irradiation.

On receipt of the patient in hospital, she had several ulcerated tumorous nodes at

the site of the right mammary gland in the post-operational scar. The additional inspection revealed the right-hand pleurisy and lymphatic edema of the right hand.

The following chemotherapy was conducted: intrapleural injection of cisplatin and two courses of polytherapy with doxorubicin and cisplatin. The condition of the patient did not improve. Respiration insufficiency remained due to continuous pleural exudation.

Thereafter the patient was treated with the complex preparation Reducin, comprising 0.1 mg of AFP, 5.0 mg of amphotericin B and 4.0 mg of polyglucin. This preparation was injected intravenously once in three days during one month (10 injections in all).

As a result of the treatment with Reducin a clear effect was achieved, which became apparent from the formation of epithelium of ulcerated skin surfaces, from the resorption of cancer infiltrate and reduction of tumorous nodes, from the decrease of lymphatic edema of the right hand. Pleural exudates no longer accumulated because of obliteration of the right pleural cavity wall. Respiratory insufficiency reduced as well. Advantageous clinic changes mentioned were achieved in a month. The condition of the patient improved, her quality of life became satisfactory. The achieved improvement of condition lasted for 2 months after the treatment with Reducin. In 6 months the patient died because of the growth of metastases in the portal fissure and insufficiency of systemic circulation.

#### Example

Patient N., 68 years old, was hospitalized with the diagnosis: ovarian cancer, multiple metastases in peritoneum.

The patient was operated on to excise the uterus and uterine appendages, but because of dissemination of metastasis process the excision of the tumor was not done. After the operation irradiation therapy was conducted, but without any effect. The condition of the patient became worse progressively: pains and cachexy increased. Laboratory findings of blood worsened. The patient refused to take chemotherapy.

The treatment with Reducin began one month after the irradiation therapy. The complex preparation Reducin, comprising 0.15 mg of AFP, 7.0 mg of amphotericin B and 3.0 mg of dextran was injected intravenously once in three days, 10 injections in one course.

After the first course of the treatment with Reducin, the patient felt better. Pains disappeared, appetite appeared. Hemoglobin level in blood normalized. The patient was taken home and she was observed at home.

In 6 months time she came for the secondary treatment with Reducin. The inspection showed that the process was stabilized. The tumor had not increased in size. The second course was conducted according to the same scheme. No side effects were registered.

The scheduled inspection after the next 6 months showed stabilization of the process. The condition of the patient was satisfactory, the patient was active, laboratory findings of blood were normal.

#### Example

Patient M., 19 years old, was hospitalized with the diagnosis: testicular cancer. The cancer had been diagnosed 4 months earlier. The patient was operated on: the right testicle carrying cancer was removed. After the operation the patient had chemotherapy (3 courses of BEP (bleomycin, etoposide, cisplatin)).

During the inspection metastases in lungs, pleura and liver were detected. Taking into account that the previous chemotherapy was ineffective and had led to serious complications (the patient had symptoms of cardiac insufficiency, edema of lower extremities) the patient was suggested to be treated with Reducin.

The complex preparation Reducin, comprising 0.1 mg of AFP, 5.0 mg of

amphotericin B and 4.0 mg of glucose was injected intravenously once in three days in a course of 10 infusions. The first injection was followed by a rise in temperature (up to 38.5°C) that was treated with standard antipyretics. The next injections of Reducin did not lead to rise in temperature. No other side effects were observed.

After the treatment with Reducin the conditions of the patient stabilized, edema of tissues reduced. The X-ray inspection of lungs showed 25% decrease of metastasis. Ultrasound of internal showed that the metastases in liver had not increased in size.

The repeated inspection 3 months later showed stabilization of the process. The condition of the patient was satisfactory.

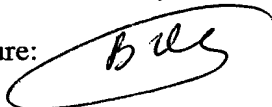
In conclusion:

The use of the complex preparation Reducin in treatment of patients with different malignant tumors and metastases have led to stabilization of the process and improvement of the condition of the patients. The decrease of the sizes of tumors and metastases was not accompanied with intoxication or increase of pains. In several cases fever was registered, but this was easily treated with standard antipyretics. No other side effects were registered during the use of Reducin. The preparation did not influence adversely laboratory findings of blood. The patients felt better and their appetite appeared. Therefore, the treatment with Reducin provides improvement in quality of life to the patients suffering from malignant tumorous process.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statement may jeopardize the validity of the application or any patent issued thereon.

Signed this 15<sup>th</sup> day of June 2004

Signature:

A handwritten signature in black ink, appearing to be 'V. Pak', enclosed within a hand-drawn oval.

Vladimir Pak